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10/717,653	11/21/2003	Thomas P. Jerussi	4821-529-999	9144

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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	PAPER NUMBER
1611	
MAIL DATE	DELIVERY MODE
02/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/717,653	JERUSSI, THOMAS P.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 11/12/08, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

This action is final.

Status of the Claims

Claims 41-51 are currently pending in this application and are the subject of the Office action.

REJECTION

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 41-51 are rejected under 103(a) as being unpatentable over Scott et al. (Scott et al. The effects of BTS 54 505, a metabolite of sibutramine, on monoamine and excitatory amino acid-evoked responses in the dosolateral geniculate nucleus in vivo. Br. J. Pharmacol., 111:97-102 (1994), in view of Young (WO 94/00114) and Adda et al. (Adda et al. Narcolepsy and depression. Arq. Neuropsiquiatr. 1997;55(3A):423-6, abstract only).

Claim 41 recites [a] method of treating narcolepsy comprising administering to a patient a therapeutically effective amount of enantiomerically pure (S)-didesmethylsibutramine, or a pharmaceutically acceptable salt thereof." Claim 42 recites "wherein the (S)-didesmethylsibutramine comprises greater than about 80 percent by weight of didesmethylsibutramine." Claim 43 recites "wherein the (S)-didesmethylsibutramine comprises greater than about 90 percent by weight of didesmethylsibutramine." Claim 44 recites "wherein the (S)-didesmethylsibutramine

comprises greater than 95 percent by weight of didesmethylsibutramine."Claim 45 recites "wherein the amount of (S)-didesmethylsibutramine administered is from about 0.1 mg to about 60 mg per day."Claim 46 recites "wherein the amount of (S)-didesmethylsibutramine administered is from about 2 mg to about 30 mg per day." Claim 47 recites "wherein the amount of (S)-didesmethylsibutramine administered is from about 5 mg to about 15 mg per day." Claim 48 recites "wherein the (S)-didesmethylsibutramine is administered orally, mucosatly, rectally, transdermally, topically or parenterally." Claim 49 recites "wherein the (S)-didesmethylsibutramine is administered orally." Claim 50 recites "wherein the (S)-didesmethylsibutramine is administered parenterally." Claim 51 recites "wherein the (S)-didesmethylsibutramine is administered intravenously, intramuscularly or subcutaneously."

Scott et al. (Scott et al. The effects of BTS 54 505, a metabolite of sibutramine, on monoamine and excitatory amino acid-evoked responses in the dosolateral geniculate nucleus in vivo. Br. J. Pharmacol., 111:97-102 (1994)) shows the general knowledge regarding didesmethylsibutramine. Scott et al. teach that the primary and secondary amine metabolites of sibutramine (i.e. BTS 54 505, or desmethylsibutramine, and BTS 54 3554, or didesmethylsibutramine) have a similar pharmacological profile to the parent compound (= sibutramine) in vivo, but are up to 100 fold more potent than sibutramine as monoamine uptake inhibitors in vitro (page 97, column 1, lines 11-16; see also Figure 1. Scott et al. teach that the in vitro data indicate that the pharmacological effects of subitramine in vivo are mainly due to the activity of its

primary and secondary amine metabolites (page 97, column 1, lines 16-20). Scott et al. also disclose that tricyclic antidepressants have a number of side effects which arise from their affinity for muscarinic cholinoceptors and histamine receptors; these side effects may limit their therapeutic use in the treatment and/or prevention of NMDA-induced toxicity and neurodegeneration (page 101, column 2, last paragraph, lines 15-21). Scott et al. further disclose that since sibutramine and its active metabolite BTS 54 505 (= didesmethylsibutramine) have no significant affinity for muscarinic receptors, $\alpha 1$, $\alpha 2$, β adrenoceptors, dopamine D1 and D2 receptors, and 5-HT1 and 5-HT receptors, sibutramine and BTS 54 505 may result in fewer and less pronounced side-effects than the tricyclic antidepressants (page 101, column 2, last paragraph, lines 21-27).

However, Scott et al. do not teach narcolepsy or pure (-) didesmethylsibutramine.

Young is added to show the general knowledge regarding the parent compound sibutramine (e.g. dosing, route of administraton) and its optically pure enantiomers and methods for preparing the same. Young discloses a method of using racemic sibutramine and optically pure (-) sibutramine for treating Parkinson's disease. Young teaches optically pure and substantially optically pure (-) sibutramine and methods of obtaining optically purified stereosiomers of sibutramine (page 4, lines 1-10; and page 17, line 34 to 32). Young teaches that optically pure (-) sibutramine possesses potent activity in treating disorders ameliorated by inhibition of neuronal monoamine reuptake (e.g. Parkinson's disease and depression) while avoiding the adverse effects associated with the administration of the racemic mixture of sibutramine (page 2, lines 2-4; page 10, lines 8-32). Young discloses that optically purified stereoisomers of sibutramine are

most readily obtained by resolving the racemic mixture of sibutramine by fractional crystallization of the diastereomeric salts formed with optically active resolving agents via a commonly used conventional process (page 17, line 34 to page 18, line 32). Young teaches that in general the recommended dose range of sibutramine is from about 1 mg to about 60 mg per day, which overlaps with the instant claimed dosage range for optically pure (-) diesmethylsibutramine (page 19, line 5-9). Young teaches an antidepressant composition for the treatment of a human in need of antidepressant therapy which comprises an amount of (-) sibutramine, substantially free of its (+) sterioisomer, wherein said of (-) sibutramine is in an amount sufficient to alleviate depression. (page 11, line 28 to page 12, line 3). Young also teaches that any suitable route of administration may be employed for providing the patient with an effective dosage of (-) sibutramine e.g. oral, rectal, parenteral, transdermal; dosage forms include tablets, troches, dispersions, suspsensions, solutions, capsules, patches, and the like (page 21, lines 7-14).

Young does not teach optically pure (-) didesmethylsibutramine or narcolepsy.

Adda et al. (Adda et al. Narcolepsy and depression. Arq. Neuropsiquiatr. 1997;55(3A):423-6, abstract only) teach that the main symptoms of narcolepsy include excessive daytime sleepiness and cataplexy and that depressive complaints are occasionally reported (abstract).

It would have be obvious to a person of skill in the art at the time the instant invention was made to use the optically pure (S) form of BTS 54 505 (= didesmethylsibutramine) as taught by Scott et al. to treat narcolepsy as taught by Adda

et al. to control symptoms of depression. One would have been motivated to treat narcolepsy with optically pure (S) BTS 54 3554 because Scott et al. teach that BTS 54 3554 (didesmethylsibutramine) has a similar pharmacological profile to the parent sibutramine compound in vivo (e.g. treating depression; page 97, column 1, lines 11-16; see also Figure 1) and that sterochemical purity is of importance in the field of pharmaceuticals since certain isomers may actually be deleterious and not simply inert (page 3, lines 23-31). One would have expected to successfully separate the (S)-didesmethylisubutramine from the (R) isomer for use to treat narcolepsy because Young teaches a well known crystallization fractionation method for separating optical isomers such as subitramine and a major portion of the chemical structure of sibutramine is identical to the chemical structure of didesmethylsibutramine (Cf. In re Kerhoven, 626 F.2d 848, 205 USPQ 1069 (CCPA 1980). In addition, Adda et al. teach that depression is observed in patients with narcolepsy; thus teaching an overlapping population. To the extent that (-)-didesmethylsibutramine has a similar pharmacological profile to the parent sibutramine compound, which is known to effective in treating depression, a person of skill in the art at the time the invention was made would have similarly expected to successfully use (-)-didesmethylsibutramine to treat the symptoms of depression, including the symptoms of depression associated with narcolepsy.

Thus, a person of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonably predictability.

Response to applicant's arguments

Applicant's argument that the cited references fail to teach or suggest the instant claimed enantiomerically pure (S) didesmethylsibutramine is not found to be persuasive because it is the examiner's position that it would have been obvious to a person of skill in the art at the time the invention was made to attempt (or try) to isolate and use the enantiomerically **pure** (S) didesmethylsibutramine form of the racemate compound as taught by Scott et al. to treat a patient with narcolepsy for its purity. Besides, Young et al. suggest that enantiomerically pure sibutramine and racemate sibutramine, which have the same core structure as the instantly claimed compound, possess the same spectrum of therapeutic activity (page 2, lines 2-4; page 4, lines 1-10; page 10, lines 8-32; and page 17, lines 34-42). One would have been motivated to do so because racemate didesmethylsibutramine as taught by Scott et al. is pharmacologically active such that an artisan skilled in the art would reasonably expect that use of the enantiomerically pure(S) didesmethylsibutramine would possess similar pharmacologic activities as that of the racemate and KSR state that **"obvious to try"** can be a motivation in cases, as in this case, where an artisan is faced with a choice of choosing from a finite number of identified options (racemate didesmethylsibutramine, or pure (S)- didesmethylsibutramine, or pure (R)- didesmethylsibutramine), which are directed to achieving predictable solutions (therapeutically pure active S-dimesthylsibutramine) with a reasonable expectation of success (MPEP 2141; see also KSR 550 US at ___, 82 US USPQ2d at 1396). Further, applicant's argument that sterochemical purity cannot be used as a basis to render the instant claims obvious is also not found to be persuasive because Scott et al. teach that sterochemical purity is of importance in the

field of pharmaceuticals (page 3, lines 23-31) and Young et al. teach a method for separating isomers such as sibutramine (page 17, line 34 to page 18, line 32) such that one would reasonably expect to successfully separate the (S) enantiomer of didesmethylsibutramine from its racemate mixture absence evidence to the contrary. In addition, Adda et al. teach that there is a nexus between narcolepsy and depressive symptoms and both Scott et al. and Young et al. teach that sibutramine compounds are useful to treat depression. Thus, an artisan skilled in the art would have expected to successfully obtain the pure (S)-didesmethylsibutramine from the didesmethylsibutramine racemate taught by Scott et al. via the isomer separation method taught by Young et al. for use to treat a patient with narcolepsy, wherein said patient have depressive symptoms associated said narcolepsy, since Adda et al. teach that there is a nexus between narcolepsy and depression and Scott et al. suggest that (S) didesmethylsibutramine may have similar properties as the racemate form (such as anti-depressive effects) and applicant has not provided any objective evidence of unexpectedness. Applicant has not specified what symptoms are treated in the scope of the claim. Thus, the treatment of depression, a symptom of narcolepsy, is a treatment of narcoplepsy.

With respect to applicant's argument that Adda et al. fail to teach or suggest the treatment of narcolepsy (because any administration of an anti-depressant would have been for the purpose of treating depression and not for the purpose of treating narcolepsy), this argument is not found to be persuasive since even though not all patients with narcolepsy have symptoms of depression it is routine in the medical arts to

treat patients based on patient factors, including severity of disease or symptoms, such that it would have been within the scope of skill and knowledge of an artisan skilled in the art to combine the cited references to treat a patient suffering from narcolepsy, wherein said patient also had depressive symptoms associated with narcolepsy as taught by Adda et al., with optically pure (S) didesmethylsibutramine to control the symptoms of depression as Adda et al. suggest that patients with narcolepsy are susceptible to develop depressive symptoms as a complication of their narcoleptic condition (abstract). Thus, it is the examiner's position that applicant's assertion that Adda et al. would have **discouraged** an artisan skilled in the art from using anti-depressants for the treatment of narcolepsy is not persuasive because patients with narcolepsy are susceptible to depression as evidenced by the teaching of Adda et al. and applicant has not provided any objective evidence to show the contrary. Besides, the instant claimed narcolepsy population does not preclude a narcolepsy patient from also developing depressive symptoms. To the extent that depressive symptoms are experienced by patients with narcolepsy, it would have been obvious to try to treat a patient with narcolepsy with optically pure (S) didesmethylsibutramine to control the symptoms of depression in said patient because Scott et al. teach that sterochemical purity is of importance in the field of pharmaceuticals (page 3, lines 23-31) and Young et al. teach a method to isolate isomers of the prior art suggest that the pure (S) didesmethylsibutramine might be preferred over the racemate form.

With respect to applicant's reliance on case law, it is the examiner's position that the facts of the instant case are distinguishable from the facts in *Rapoport v. Dement*

since in the instant case the symptom of depression is not severable from narcolepsy but is related to the underlined narcopletic condition such that one would reasonably expect to successfully control the symptoms associated with narcolepsy (e.g. depression) with optically pure (S) didesmethylsibutramine absent objective evidence to the contrary (see applicant's Response, page 4, last full para. to page 6, last full para.).

Thus, the rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

26 January 2009

/C. R./

Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611